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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/888,734	06/25/2001	Bruce Joseph Roser	GJE-6089D1	2528

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GAINESVILLE, FL 326066669

EXAMINER

PRATS, FRANCISCO CHANDLER

ART UNIT	PAPER NUMBER
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1651

DATE MAILED: 02/24/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	<b>Application No.</b> 09/888,734	<b>Applicant(s)</b> ROSER, BRUCE JOSEPH	
	<b>Examiner</b> Francisco C Prats	<b>Art Unit</b> 1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

- 1) ☒ Responsive to communication(s) filed on 08 December 2003.
- 2a) ☐ This action is **FINAL**.                      2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

- 4) ☒ Claim(s) 14-16 and 20-22 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 14-16 and 20-22 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All    b) ☐ Some \*    c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

- |  |   |
|--|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)  | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

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**DETAILED ACTION**

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on December 8, 2003, has been entered.

The terminal disclaimer filed on December 8, 2003, disclaiming the terminal portion of any patent granted on this application which would extend beyond the expiration date of application serial number 08/875,796, now U.S. Pat. 6,649,386, has been reviewed and is accepted. The terminal disclaimer has been recorded.

Claims 14-16 and 20-22 are pending and are examined on the merits.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

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(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 14 and 16 are rejected under 35 U.S.C. 102(e) as being anticipated by Curtis et al (U.S. Pat 5,824,780).

The '780 patent describes a process of producing an activated and stabilized Factor VIII in the absence of albumin. See claim 1, at column 9. The Factor VIII is clearly separated from albumin, as evidenced by the removal of "other proteins" from the Factor VIII preparation. See step (b) of claim 1, at column 9, line 46 through column 10, line 3. The Factor VIII is stabilized by the addition of a stabilizing additive which may be trehalose. See claim 4, at column 10. Note the recitation of trehalose and albumin as alternative stabilizing additives. The '780 patent also describes that after preparation of the stabilized solution of Factor VIII, the Factor VIII is lyophilized. See claim 5, at column 10.

See also, the discussion at col. 5, lines 30-43, stating that "[e]xamples of stabilizers include albumin ... and trehalose", and that "[f]ollowing preparation and stabilization of the activated Factor VIII, the protein can be lyophilized and

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stored at reduced temperatures ...." Col. 5, lines 4-6. Note that the '780 patent lists recombinant Factor VIII as being suitable for use in the disclosed process. Column 2, lines 61, et seq. Thus, taken as a whole, the '780 patent clearly describes a process wherein an aqueous solution of Factor VIII in the absence of albumin is lyophilized in the presence of trehalose, are cited in the claims.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 14-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Curtis et al (U.S. Pat 5,824,780) in view of Livesey et al (U.S. Pat. 5,364,756).

As discussed above, the '780 patent, by virtue of the specific embodiments recited in the claims, describes the preparation of albumin-free Factor VIII, as well as the lyophilization of the enzyme and the use of trehalose as a

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stabilizer. Even if one considers the '780 patent as not being anticipatory of claims 14 and 16, the artisan of ordinary skill reading only the '780 patent clearly would have been motivated to have lyophilized an albumin-free preparation of Factor VIII in trehalose.

The '780 patent differs from the claims under examination by failing to describe the lyophilization of native Factor VIII, as recited in claim 15. However, Livesey clearly provides motivation for lyophilizing "native" Factor VIII in trehalose without albumin by not only claiming a specific embodiment (claim 17) of lyophilizing Factor VIII, but also disclosing that trehalose, and not albumin, is one of a number of agents particularly suited to dry preservation of macromolecules such as proteins. See col. 9, lines 16 -32:

For example, trehalose and polyhydroxyl carbohydrates bind to and stabilize macromolecules such as proteins and nucleic acids in a virus or vaccine sample when dried, thereby protecting the integrity of the sample. Various dry protectants can be used in the present invention: sucrose, raffinose, trehalose, zinc, proline (or other protein stabilizers), myristic acid (a known thermostabilizer of vaccines), spermine (a polyanionic compound) and combinations thereof.

Thus, the artisan of ordinary skill seeking to preserve the "native" Factor VIII encompassed by Livesey's claim 17, recognizing that Factor VIII is a protein, clearly would have looked to trehalose instead of albumin, based on Livesey's

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disclosure that trehalose is one of a number of agents particularly suited for protein protection in freeze-drying procedures, and albumin is not. Additional motivation for freeze-drying Factor VIII using trehalose in the absence of albumin would have been derived from the fact that the lone example of protein freeze-drying of Livesey, Example 5 at columns 23 and 24, demonstrates that the integrity of a protein-containing viral vaccine is adequately protected by trehalose in buffer with no other preservative agents.

Claims 14-16 and 20-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Curtis et al (U.S. Pat 5,824,780) in view of Livesey et al (U.S. Pat. 5,364,756) as applied to claims 14-16 above, and further in view of Bhattacharva et al (U.S. Pat. 5,288,853).

As discussed above, the '780 patent and Livesey clearly provide motivation for lyophilizing an aqueous solution of albumin-free Factor VIII, recombinant or native, in the presence of trehalose. While neither reference directly describes the use of histidine in the lyophilization milieu for Factor VIII, Bhattacharva clearly discloses that histidine is a preferred buffer for use in Factor VIII preparations to be lyophilized. See column 7, lines 19-22. ("Histidine is preferred as a buffer

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in the purification, since the final lyophilized Factor VIII is more easily resolubilized when it is in a buffer comprising histidine.") Thus, the artisan of ordinary skill, recognizing the advantages of including histidine in the lyophilization milieu for Factor VIII, clearly would have been motivated to have included histidine the aqueous solutions used in the processes of Curtis and/or Livesey. A holding of obviousness is therefore required.

#### ***Response to Arguments***

All of applicant's argument has been fully considered but is not persuasive of error. As noted above, the newly cited '780 patent provides explicit disclosure of embodiments reading on certain of applicant's claims, and is therefore considered to anticipate those claims.

Regarding the Livesey reference, it is noted, as argued by applicant, that Livesey's process includes the step of freeze-drying small droplets produced by nebulization. However, contrary to applicant's argument, the droplets in fact consist of aqueous solutions. Moreover, the claims under examination herein do not exclude the use of nebulizing steps as described by Livesey. At the very least, Livesey makes it clear that albumin-free native Factor VIII is readily freeze-dried using



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trehalose as a cryoprotectant, thus further suggesting that the methods of Curtis would also be readily applicable to native Factor VIII.

As to lack of motivation present in the cited art, as urged by applicant, the simple fact is that the claims are directed to freeze-drying a therapeutic protein known to be desirably freeze-dried, in the presence of a notoriously well known cryoprotectant, trehalose. At the very least the claims and disclosure of the '780 patent at col. 5, lines 30-43, provide direct motivation for adding trehalose to an aqueous solution of Factor VIII, and lyophilizing the resulting solution. The additional disclosure of Livesey, verifying trehalose as a cryoprotectant suitable for use in a lyophilization milieu, makes it clear freeze-drying proteins such as Factor VIII in the presence of trehalose, but in the absence of albumin, clearly would have been considered obvious at the time of applicant's invention. Because applicant has not demonstrated any unexpected result commensurate in scope with the claimed subject matter, it is respectfully submitted that allowance of the pending claims clearly would be improper.


No claims are allowed.

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Any inquiry concerning this communication or earlier communications from the examiner should be directed to Francisco C Prats whose telephone number is 571-272-0921. The examiner can normally be reached on Monday through Friday, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

  
Francisco C Prats  
Primary Examiner  
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FCP